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Discrimination of Biomolecular Conformation Using the Scanning Kelvin Probe Technique

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The burgeoning disciplines of genomics and proteomics require the sensitive and specific discrimination of biomolecular interactions in high throughput microarray format. Ideally, the detection technique selected would be a direct measure of specific interactions without the use of exogenous labels, and be readily incorporated into a scanning array format. Using scanning Kelvin probe technology to measure inherent electrical properties associated with biomolecular interactions, we have been able to discriminate fully complementary nucleic acid hybridization and the presence of single nucleotide polymorphisms (SNP's). Variations in work function, measured as contact potential difference (CPD), of single-stranded DNA (ssDNA), double-stranded DNA (dsDNA) and dsDNA with internal mismatches in an array format on gold-coated silicon chips were clearly distinguished under ambient conditions without the use of an external label. In this study, it is estimated that the DNA density on the gold-coated wafer surface is in the picomolar/cm² range since thiolated oligomers were immobilized without the presence of Mg⁺⁺ in the buffer solution. We propose that the selective discrimination of DNA hybridization by Kelvin probe analysis is due to a change in biomolecule conformation, polarizability, and dielectric properties of the DNA oligomer layer, and that these parameters are characteristic of discrete molecular interactions. The scanning Kelvin probe (SKP) technique described here can easily discern DNA hybrids, both fully complementary and mismatched, formed in physiological buffer, and measured under ambient conditions at room temperature. SKP analysis can be readily adapted for high-throughput, microarray formats; it provides a significant advantage over current detection methods due to the elimination of exogenous labeling and the capability of discriminating subtle differences in molecular conformation.